REMARKS

Applicant traverses the rejections of claims 2, 7, 8, 10 and 21-28 as being unpatentable as obvious under 35 U.S.C. 103(a) over Boyce et al. U.S. Patent Number 6,294,187 in view of the combination of Sander et al. 5,356,629 and Breitbart et al. U.S. Patent Number 5,700,289.

The amendment to claim 21 deletes "a" as it refers to "particles" which are plural while the amendment to claim 23 corrects an antecedent inconsistency as "said hydrogel" refers back to "chitosan" and claim 27 "allograft" refers back to claim 23, allograft bone having been previously present in claim 27.

The present invention is directed toward a formable putty type sterile implant composition having a chitosan or alginate carrier containing milled demineralized bone particles which can be formed by the surgeon in the operating room and placed into the bone defect site to promote bone growth at the defect site.

The Boyce '187 patent (noted as primary art) simply teaches a shaped hardened load bearing osteoimplant bone structure formed of compressed bone particles and not powdered demineralized bone particles mixed in a carrier forming a formable putty composition.

Compressive forces typically ranging from about 2,500 to 60,000 psi are applied to bone particles in a press-mold to produce a hard chalk-like material. (Col 11, lns 65-66) The material can then be easily shaped or machined into any of a wide variety of configurations. It should be specifically noted that in the preferred embodiment, the osteoimplant is provided with macro porosity, i.e. holes which enhance blood flow through the osteoimplant or the holes can be filled with a medically useful substance such as Grafton putty. As noted in the '187 patent the resulting osteoimplant can assume a determined or regular form or configuration such as a sheet, plate, disk,

cone, pin, screw, tube, tooth, tooth root, bone or portion of bone, wedge or portion of wedge, cylinder, threaded cylinder (dowel) to name but a few. Of course, the osteoimplant can be machined or shaped by any suitable mechanical shaping means. In the preferred embodiment, the osteoimplant possesses the configuration of a threaded cylinder (dowel) (Col 14, lns 6-16) . It is also noted that the osteoimplant is applied at a bone repair site which requires mechanical support (Col 14, lns 21-25) and can be implanted using any suitable affixation means, c.g., sutures, staples, bioadhesives, and the like. (Col 14, lns 49-51)

The Boyce et al '187compressed bone structure is formed by applying compressive force of at least about 1000 psi, has a bulk density greater than about 0.7 g/cm^3 and a wet composite strength substantially exceeding 3MPa to form a hardened mass. The bone particles which are used in the hardened structure are formed by milling whole bone to produce fibers, chipping whole bone, cutting whole bone, fracturing whole bone in liquid nitrogen or otherwise disintegrating the bone tissue. The bone particles range in average particle size from about 0.05 to about 1.2 cm in size and possess an average median length to median thickness of from about 1:1 to about 3:1. **Alternatively or in combination with the previously mentioned bone powder**, bone particles generally characterized as elongate and possessing relative high median length to median thickness ratios are utilized. The elongate particles are obtained by milling or shaving the surface of an entire bone with at least 60%, preferably 90% of the bone particles being elongated. These elongated particles possess a medium length from about 2 to 200 mm and preferably from about 10 to about 100mm. These elongate bone particles can possess a median length to median thickness ratio of at least about 50:1 up to about 500:1 or more. **Preferably, at least about 60 weight percent, more preferably at least about 75 weight percent and most preferably at least about 90 weight percent of the bone particles**

utilized in the preparation of the bone particle-containing composition are elongate. It is noted that elongate bone particles provide an osteoimplant possessing particularly good compressive strength. It can thus be seen that the characterization of the Examiner that the sizes of the bone particles used in Boyce et al '187 correspond to that of the present invention is not correct. Furthermore there is no way that Boyce et al '187 could be characterized as formable. The composition fabricated in accordance with the Boyce et al '187 disclosure more preferably has a bone particle content ranging from about 50 to about 95 percent based on the weight of the entire composition.

As noted in the Examples of Boyce et al '187; the bone particles were mixed with different solutions such as glycerol (Examples 1, 12), cross linked with formalin (Examples 2 and 3), saline (Example 4), ethanol and ethyl cellulose (Examples 5, 6, 7, 8), and water (Examples 9, 10, 11),. There is no teaching in the examples of the carrier of the present invention, the bone particle range, the weight of the carrier and range of the same, viscosity or any concentration of cellular material (Boyce et al '187 being a solid and having no viscosity). Applicant would point out that the use of hydrogels, are disclosed only as a thickener when water and/or glycerol are used as the wetting agent for forming the slurry. These hydrogels are used to suspend and keep the bone particles separate during the application of the compression forces to form the solid structure and do not act as a carrier for the bone particles.

Chitosan is noted in Boyce et al '187 as a binder or an adhesive for the demineralized bone particles and is incidentally found as one of a 60+ line list of suitable binders or adhesives. (Col. 8, lns. 13-40) Preferred binders are polyhydroxybutyrate, polyhydroxyvalerate and tyrosine-based polycarbonates. When employed, binders will typically represent from about 5 to about 70 with

percent of the bone particle-containing composition calculated prior to compression of the composition.

Boyce et al '187 also envisions the use of fibers which will typically represent from about 5 to about 75 weight percent of the bone particle-containing composition. Chitosan is also noted as a thickener to be used when the wetting agent is water and/or glycerol to preclude premature bone particle separation and improve suspension keeping characteristics of the composition (Col. 10, lns. 58-67 to Col. 11, lns. 1-10) prior to application of the compressive forces. This is used to keep the bone particles separate during application of the compressive forces to form the solid structure and not as a carrier for the bone products which is then directly applied to the wound site. Chitosan is not noted as being use or in any of the Examples or in any of the preferred embodiments.

The Boyce et al '187 composition is heated in a mold during or after the compression step at a suitable temperature ranging from about 30° to about 70° C from 1 to 72 hours preferably 24 to 48 hours. Optionally it can be cross linked to improve the mechanical strength of the osteoimplant. Thus it is apparent that prior to final manufacturing steps of molding, heating and cutting the osteoimplant is not usable for application of a surgeon in the operating room.

The Boyce et al '187reference cannot be combined with Sander '629 and/or Breitbart et al. '289 and does not teach or suggest the composition of the present invention in connection with the teachings of the Sander '629 patent and/or Breitbart et al. 289.

The Sander et al. '629 reference (noted as secondary art) discloses the making of a bone cement to fill defects in bone. The Examiner has argued that the '629 reference teaches (1) composition for bone repair comprising particles dispensed in a matrix; (2) can be implanted into defective bone tissue; (3) discloses the use of drugs and other substances that can induce bone

growth; (4) biocompatible particles of any size can be used int the composition and (5) matrix material can conveniently comminuted to appropriate particle size.

The bone cement of Sander et al '629is formed by mixing biocompatible particles preferably polymethylmethacrylate coated with polyhydroxyethylmethacrylate (Examples 1 , 2 and 5 - 10) or particles of glycolide-lactide copolymer (Examples 3 and 4) in a matrix to obtain a molded semi-solid mass which can be suitably worked for implantation into bone. The biocompatible particles which are dispersed in the matrix can be formed from either bioabsorbable or nonbioabsorbable material. Suitable nonbioabsorbable material which can be used to form the biocompatible particles can be derived from xenograft bone, homologous bone, autogenous bone, hydroxyapatite and polymethylmethacrylate coated with polyhydroxyethylmethacrylate, the preferred nonbioabsorbable material.. The weight of the nonbioabsorbable material in the wetted composition of Sander et al '629 runs from 35% to 75% (Dry weight 64% to 94%); to most preferably 45% to 60% (Dry weight 73% to 92%) with the more preferred weight being 40% to 70% (Dry weight 82% to 90%)(Col 4 lns 21 - 30). **There is no disclosure of demineralized bone used as the nonbioabsorbable material, in Sander et al '629 and demineralized bone is used as an additive in the nature of an osteogenic agent.** This bioactive substance is included as one or more medico-surgically useful substances such as a therapeutic agent, a growth promoting factor and osteogenic agent. It is noted in Col. 4 ln 40 to Col. 5 ln 17 that a bioactive substance can be introduced into the compositions, either directly into the matrix prior to or after wetting or into the biocompatible particles or polymethylmethacrylate particles, the preferred substance being polymethylmethacrylate. A growth promoting factor can be introduced into the composition such as fibroblast growth factor, bone growth factor, epidermal growth factor, platelet derived growth factor, macrophage derived growth

factor, alveolar derived growth factor, monocyte derived growth factor, magainin and so forth. The bioactive substance can also be an osteogenic agent such as osteoinductive protein, demineralized bone powder, in addition to morselized cancellous bone, aspirated bone marrow and other autogenous bone sources. As previously noted demineralized bone powder **is an additive of undetermined amount** and is included in a general laundry list and is not taught to be the biocompatible material, but rather an osteogenic agent.

In Examples 1 and 2 of the '629 patent polymethylmethacrylate particles were coated with polyhydroxyethylmethacrylate carboxymethylcellulose or methylcellulose and water' Examples 3 and 4 use particles of glycolide-lactide copolymer; Examples 5 and 6 use particles of polymethylmethacrylate coated with polyhydroxyethylmethacrylate hydroxypropylmethylcellulose water; and Examples 7-10, use particles of polymethylmethacrylate coated with polyhydroxethylmethacrylate. The preferred nonbioabsorbable material was mixed with a matrix **HA having a molecular weight of about six hundred thousand Daltons.** Indeed **in all of the Examples no bone material of any type is used.** The use of demineralized bone in the range noted present invention results in an osteoinductive material which promotes bone growth.

Sander et al. '629 has a matrix (cellulose ether, collagen, hyaluronic acid, pharmaceutically accepted salt of hyaluronic acid, derivative of hyaluronic acid and pharmaceutically acceptable salt of hyaluronic acid derivative and mixtures thereof)ranging from 6% to 36% by weight with 64% to 94% by weight of polymethylmethacrylate crystals. If one were to substitute demineralized bone material for the polymethylmethacrylate coated with polyhydroxyethacrylate of Sander et al '629, which substitution is not taught or suggested by this reference and is a completely different material, the range would be outside of the inventive range claimed..

Sander et al. '629 does not teach or obviate the present invention alone or combined with the other cited references. Use of (1) demineralized bone material as the nonbioabsorbable material and as a major component of the composition; (2) an equivalent biocompatible material weight, (3) a carrier of chitosan or alginate; (4) a molecular weight or the carrier which is the same as the molecular weight of the inventive carrier; (5) a phosphate buffer to neutralize the composition, and (6) the addition of cellular material at a concentration of 10^5 to 10^8 per cc of the carrier is not taught or disclosed. Furthermore Sander et al is not osteogenic relying on antigenic response.

The '629 reference does not suggest using demineralized bone together in a buffered isotonic salt carrier with a neutral osmolality or that such a combination is osteoinductive and medically beneficial in the repair of bone tissue. The Examiner's inference that the '629 patent teaches that the composition can comprise living cells such as erythrocytes, leucocytes and endothelial cells and that the pH of the composition is approximately 6.8-7.4 is not based on the teachings of the '629 patent and is a hind site supposition.

The Breithart et al '289 patent (noted as secondary art) is directed toward a sponge like matrix preferably constructed of a biodegradable, biocompatible synthetic polymer which uses the patient as the source of cells for the repair of bone defects. The cells are taken from the periosteum, (consisting of mainly multipotent mesodermal cells), isolated and seeded onto and into a matrix. In other embodiments, the matrix is formed of a material such as hydroxyapatite or mixtures of hydroxyapatite and polymer, or tricalcium phosphate. The matrix can also be sterilized bone or a porous metal alloy. The Examiner notes that Breithart et al '289 teaches (1) the use of alginate and chitosan: In regard to the disclosure of alginate and chitosan, in col. 6, lns. 20-40 a large laundry list (over 30 polymers) of potential natural and synthetic polymers are noted which can be used to form

the fibrous matrix. Examples of natural polymers includes polysaccharides such as alginate. (Col. 6 ln 38) It is quite apparent that the matrix is solid as it is preferably made of hydroxyapatite, tricalcium phosphate, sterilized bone or metal alloy. In col. 10, lns. 7-10, the hydrogel which is noted is cross linked to form a three dimensional open-lattice structure includes alginate. In col. 10, lns. 43-45 alginate is disclosed as being used for hybridonia cell encapsulation, which has nothing to do with the present invention. In col. 11, lns. 27-40, chitosan is only noted for being a natural polycation such as the polysaccharide, chitosan. (Chitosan is not used as a carrier but as a cation) This is but one of a number of varieties of polycations which complex and stabilize the polymer hydrogel into a semipermeable surface membrane. Various examples are noted and it is off handedly noted, that there exists natural polycations such as the polysaccharide chitosan.

(2) cells such as mesenchymal stem cells, chondrocytes and mesenchyma cells as the ingredients forming: The patent to Breitbart et al. '289 is directed toward periosteum cells seeded into a matrix (preferably a synthetic polymer) for repair of the bone defect. The '289 patent does disclose stem cells, chondrocytes and mesenchyma cells as follows: Col. 2, lns. 45-60, it notes that prior art shows the use of autologous cells and chondrocytes attaching to hydroxyapatite. Col. 4, lns. 25-30 discloses the use of periosteum which consists of multipotent mesodermal cells. Col. 14, ln. 60 Claim 9 refers to periosteum cells seeded in biocompatible matrix.

Furthermore, none of the cited references disclose the additives of cells at a concentration of 10^5 - 10^8 per cc of carrier or a specific amount of growth factor added 10cc of carrier'

In cases which are similar to the present circumstances, the courts have ruled that beyond looking at the prior art to determine if it suggests doing what the inventor has done, one must consider if the prior art provides an expectation of succeeding in the endeavor. *In re Dow Chem.,*

837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988), "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. As noted by the court in the case of *In re Clinton,* "Obviousness does not require absolute predictability, but a reasonable expectation of success is necessary." *In re Clinton,* 527 F.2d 1226, 1228, 188 U.S.P.Q. 365, 367 (C.C.P.A.1976).

As noted by the Court in the case of *In re Gordon,* the mere fact that a prior art reference could be modified to achieve the claimed invention does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon,* 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir.1984); see also *In re Laskowski,* 871 F.2d 115, 117, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989), and *Ex parte Levengood,* 28 U.S.P.Q.2d 1300, 1302 (Bd. Pat. App. & Int. 1993). Applicants respectfully submit that is there is not any suggestion showing the desirability to arrive at the claimed structure of the present invention.

The court in *Minnesota Mining & Manufacturing Co. v. Johnson &Johnson Orthopaedics, Inc.,* 24 USPQ2d 1321 (Fed. Cir 1992) held that: "Although [a patent's] specific claims are subsumed in [a prior art reference's] generalized disclosure..., this is not literal identity." The *Minnesota* court held that the reference's ranges were so broad as to be meaningless, and provided no guidance on how to construct a product with the patented invention's benefits. The court in *In re Baird,* 29 USPQ2d 1550 (Fed. Cir. 1994) held that "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." The *Baird* court further held that a disclosure to numerous compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.

None of the cited references singularly or in combination teach or obviate the present invention and indeed the references cannot be combined. The Examiner has engaged in hind site and conjecture using unrelated bits and pieces of the discussed prior art to combine the cited prior art references and reject the present invention.

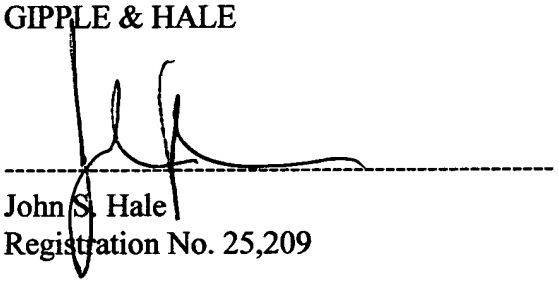
A One Month Extension of Time together with fee and a Notice of Appeal together with fee are attached to this Amendment

If any additional charges are required, please charge Deposit Account Number 07-1340.

It is respectfully requested that the arguments and amendments present in the present application in condition for favorable reexamination and that the application be passed to issue.

Respectfully submitted,

GIPPLE & HALE



John S. Hale
Registration No. 25,209

6665-A Old Dominion Drive
McLean, Virginia 22101
(703) 448-1770 ext. 304
Attorney Reference: X-9468